Research in Developmental Disabilities 33 (2012) 1541–1550

Contents lists available at SciVerse ScienceDirect

Research in Developmental Disabilities

Review article

Vitamin D and autism: Clinical review

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ARTICLE INFO

Article history:
Received 9 February 2012
Accepted 13 February 2012
Available online 21 April 2012

Keywords:
Autism
ASD
Vitamin D
Calcitriol
Calcidiol
Neurodevelopment
Brain
Gene regulation

ABSTRACT

Background: Autism spectrum disorder (ASD) is a complex neurodevelopmental disorder with multiple genetic and environmental risk factors. The interplay between genetic and environmental factors has become the subject of intensified research in the last several years. Vitamin D deficiency has recently been proposed as a possible environmental risk factor for ASD.
Objective: The aim of the current paper is to systematically review the research regarding the possible connection between ASD and vitamin D, and to provide a narrative review of the literature regarding the role of vitamin D in various biological processes in order to generate hypotheses for future research.
Results: Systematic data obtained by different research groups provide some, albeit very limited, support for the possible role of vitamin D deficiency in the pathogenesis of ASD. There are two main areas of involvement of vitamin D in the human body that could potentially have direct impact on the development of ASD: (1) the brain (its homeostasis, immune system and neurodevelopment) and (2) gene regulation.
Conclusion: Vitamin D deficiency – either during pregnancy or early childhood – may be an environmental trigger for ASD in individuals genetically predisposed for the broad phenotype of autism. On the basis of the results of the present review, we argue for the recognition of this possibly important role of vitamin D in ASD, and for urgent research in the field.

Contents

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doi:10.1016/j.ridd.2012.02.015

1. Introduction

Autism spectrum disorder (ASD) is a complex neurodevelopmental disorder with multiple genetic and environmental risk factors (Cannell, 2010; Coleman & Gillberg, 2011). There is no agreement as to whether ASD prevalence is genuinely on the rise or if a higher reported rate in recent years might be secondary to better awareness, changing diagnostic trends and more sensitive diagnostic system (Coleman & Gillberg, 2011). However, gene–environment interaction has recently become the focus of intensified ASD research (Freitag, Staal, Klauck, Duketis, & Waltes, 2010).

Among several proposed epidemiological influences on the development of ASD are the (a) much higher monozygotic (60–90%) than dizygotic (0–10%) twin concordance rates (Lichtenstein, Carlström, Rastam, Gillberg, & Ancharsater, 2010; Muhle, Trentacoste, & Rapin, 2004); (b) large variability of phenotypic expression (even among monozygotic twins) (Lundström et al., 2012), (c) distinct gender ratio (2–4 males to 1 female) (Nygren et al., 2011); (d) relationship between autism and immune dysfunction (Coleman & Gillberg, 2011); and (e) much increased rate of ASD among dark skinned children living at Northern latitudes (Barnevik-Olsson, Gillberg, & Fernell, 2008; Cannell, 2008; Eyles, 2010; Gillberg, Schaumann, & Gillberg, 1995; Goodman & Richards, 1995; Keen, Reid, & Arnone, 2010) that has led researchers to begin to address the potential role for Vitamin D in autism.

Vitamin D deficiency – either during pregnancy or early childhood – has recently been proposed as a possible environmental risk factor for ASD (Cannell, 2008; Grant & Soles, 2009). Interesting results, both at the molecular level and in animal experiments, begin to indicate the possible mechanisms for this potential risk.

Neurotoxins in the environment have been steadily on the rise, either in the form of industrial waste polluting soil, rivers and oceans, or in the form of additives in food and thousands of synthetic chemicals in materials of everyday life (Grandjean & Landrigan, 2006; Landrigan, 2010). Vitamin D deficiency has become common due to an increasingly urbanized lifestyle, rising rates of obesity, and recommendations to avoid sun exposure promulgated since the 1980s (Bosomworth, 2011; Cannell et al., 2008; Holick, 2005; Schwalfenberg, 2007). Moreover, at northern latitudes (e.g., in Scotland at 55°–61°N), sunlight with the ultraviolet B fraction is available only during a limited period of the summer. Dark skinned individuals require about 5–10 times longer exposure to sunlight to produce vitamin D compared to fair skinned individuals (Clemens, Adams, Henderson, & Holick, 1982). Therefore, when moving to northern countries, those with dark skin run the risk of not reaching satisfactory vitamin D levels.

Vitamin D has a unique role in brain homeostasis, embryogenesis and neurodevelopment, immunological modulation, (including the brain's own immune system), ageing, and also, importantly, in gene regulation (Sigmundsdottir, 2011; Harms, Burne, Eyles, & McGrath, 2011; Ramagopalan et al., 2010). In addition to these effects, vitamin D is now believed to be involved in numerous other functions in the organism. To date, it has been shown to bind to more than 2700 genes and to regulate the expression of more than 200 of them (Ramagopalan et al., 2010). Vitamin D is also known to be involved in healing processes by reducing the risk of cells becoming malignant (Sigmundsdottir, 2011).

1.1. Vitamin D: definition, biosynthesis and role in metabolism

Vitamin D is not really a vitamin, since it is produced in the body by a cascade of chemical transformations, commencing with a key photochemical reaction in the skin on exposure to the ultraviolet rays of the sun, followed by a series of further chemical transformations. Its receptors have been found in many tissues and organs. The biosynthesis of calcitriol, the active form of vitamin D of vertebrates, starts from its prime precursor 7-dehydrocholesterol, which first undergoes the key photochemical electrocyclization reaction in the skin, producing an intermediate that is spontaneously converted into **calciferol** (vitamin D_3), or cholecalciferol to be precise and to emphasize its chemical relation to cholesterol. Since the first reaction requires irradiation with UV light (at 290–315 nm), it can only proceed in the skin, e.g., within the reach of the UV rays. Cholecalciferol is then transported to the liver, where it is hydroxylated in the side-chain (at position 25) to produce **calcidiol** [25-hydroxycalciferol, 25(OH)D, or cholecalcidiol]. Finally, the latter compound is transported to the kidneys, where it is further hydroxylated (at position 1α) to finally produce **calcitriol** [1,25-dihydroxycalciferol, $1,25(OH)_2D$, or cholecalcitriol], the active compound (Feldman & Pike, 2011; Fiester & Fieser, 1959). The levels of the enzyme required for the final hydroxylation are controlled by parathyroid hormone, whose secretion is, in turn, triggered by low concentrations of calcium or phosphate (Cheng, Levine, Bell, Mangelsdorf, & Russell, 2004; Holick, Tian, & Allen, 1995). The latter enzymatic hydroxylation reaction, producing calcitriol, has also been found to occur in lymphocytes and in the brain in microglia (Eyles, Smith, Kinobe, Hewison, & McGrath, 2005).

For the sake of simplicity and to avoid confusion, which is widespread in the literature, we will use the following nomenclature for the vitamin D family originating from 7-dehydrocholesterol: **calciferol** for cholecalciferol (vitamin D_3), **calcidiol** for 25-hydroxy-cholecaciferol, and **calcitriol** for 1,25-dihydroxy-cholecalciferol. Where the literature does not discriminate, we will refer to **vitamin D** in general.

The best known role of vitamin D is to facilitate calcium and phosphate absorption in the intestine, impacting directly on the formation of the bones and their density. Vitamin D in the body follows first-order mass action kinetics (Holick, 2005), which means that at serum levels lower than 20 ng/ml (50 nmol/L) the majority of ingested or sun-derived vitamin D is immediately diverted to metabolic needs, namely bone formation, leaving nothing to its higher functions within the brain, immune system, or gene regulation.

There are two main areas of involvement of vitamin D in the human body, which may have direct impact on the development of ASD: (1) the brain (its homeostasis, immune system and neurodevelopment) and (2) gene regulation.

The aim of the current paper is to review the research findings regarding the connection between ASD and vitamin D.

2. Methods

A literature search covering the period January 1 1995 through October 31 2011 was made in PubMed, the Web of Knowledge, EBSCO OVID, MEDLINE, PsycARTICLES, Psychology and Behavioural Sciences Collection, PsycINFO, SocINDEX databases with Full Text Number of Hits.

The search strategy was as follows: vitamin d or vitamin D or ergocalciferol or vitamin d2 or vitamin D2 or vitamin d 2 or vitamin D 2 or cholecalciferol or vitamin d3 or vitamin D3 or vitamin d 3 or vitamin D 3 or calcitriol or vitamin 1,25 D3 or vitamin 1,25 d3 or vitamin 1,25 D 3 or vitamin 1,25 d 3 or calcidiol or vitamin 25 D or vitamin 25D or 25 hydroxy vitamin d or 25-OHD or 25-hydroxyvitamin D or 25 hydroxyvitamin D or 25 hydroxy vitamin d or 25 hydroxyvitamin D AND autism or autism spectrum disorder or ASD or Asperger.

We first present the results of this systematic review. We then present a narrative review of some of the other literature regarding the role of vitamin D in the human body as it could potentially relate to ASD.

3. Results

3.1. Systematic review

A systematic literature search yielded 35 articles from PubMed that dealt directly with autism and vitamin D in one way or another. Only four studies have looked at vitamin D serum levels in human subjects with diagnosed ASD or their mothers (Table 1). Nine further studies reported on nutritional deficiencies (including vitamin D) in ASD.

3.1.1. Autism – vitamin D: plasma vitamin D-levels in individuals with autism and their family members

Three studies investigated plasma levels of vitamin D directly in individuals with autism.

Meguid, Hashish, Amwar, and Sidhom (2010) reported a cohort of Egyptian children with ASD having significantly lower levels of both calcidiol (28.5 ng/ml) and calcitriol (27.1 ng/ml) as well as lower calcium serum values compared to healthy controls. The season of birth in relation to vitamin D and autism was also taken into account but no significant difference was found for the month or season of birth in either group. This was the only study that measured plasma levels of vitamin D in both children with autism and a suitable control group.

Table 1
Studies measuring plasma levels of vitamin D.

Study	*N* (case/control)	Design (limitations)	Mean/Median plasma levels of vitamin D (ng/ml)
Meguid et al. (2010) Egypt	112 (70/42)	Case – Control, Cross – sectional Children – Egyptian boys and girls with autism 2–8 years	Significant difference *Cases*: 28.5 ng/ml *Controls*: typically developing children 40.1 ng/ml
Molloy et al. (2010) USA	89 (49/40)	Case – Control, Cross – sectional Children – Caucasian boys with autism 4–8 years	No significant differences *Cases*: 20 ng/ml *Controls*: boys with acute inflammation 17 ng/ml. ALL PARTICIPANTS <31 ng/ml
Humble et al. (2010) Sweden	117 (117/0)	No controls, Cross – Sectional Adults – European white males and females with psychiatric disorder incl. autism	Adequate values in only 15% of all patients Cases with autism lowest levels: 12.6 ng/ml
Fernell et al. (2010) Sweden	80 (40/40)	Case – Control, Cross – Sectional Adults – mothers of Somali or Swedish origin with a child with or without autism	Significant difference Somali vs. Swedish mothers Trend lower values autism vs. non-autism *Cases*: Somali mothers with autism child 6.7 ng/ml; Swedish mothers with autism child 24.8 ng/ml *Controls*: Somali mothers with non-autism child 9.6 ng/ml; Swedish mothers with non-autism child 20.7 ng/ml

Note: Severe deficiency <10 ng/ml; deficiency 10–20 ng/ml; inadequacy 20–30 ng/ml; recommended 30–100 ng/ml (Humble et al., 2010).

Molloy, Kalkwarf, Manning-Courtney, Mills, and Hediger (2010) compared the actual plasma calcidiol levels in a cohort of Caucasian boys with ASD diagnosis (4–8 years old) and a group of age-matched typically developing comparison boys having intravenous catheters placed for outpatient tonsillectomies. There were no differences observed in the levels between participants with ASD and controls, but the majority of all children in this cohort (61%) had very low vitamin D levels (<20 ng/ml or <50 nmol/L). An important limitation of this study was that the control group children were all suffering from some form of acute inflammation, which could potentially affect the plasma vitamin D results (Molloy et al., 2010).

Humble, Gustafsson, and Bejerot (2010) tested vitamin D levels in adult outpatients with a range of psychiatric disorders and found that those with a diagnosis of autism or schizophrenia had significantly lower levels than other groups. This study demonstrated a considerable improvement in several patients of some of their psychiatric symptoms, e.g., psychosis and depression, with vitamin D treatment. However, there are some limitations of this study as there is very little information on details of the treatment, and there was no control group.

Although these results regarding plasma vitamin D levels in children and adults with autism appear conflicting, of the three studies, two are subject to significant methodological problems. The Molloy study suffered from the fact that the control children were likely to have had some degree of inflammation, which could have affected the vitamin D levels. The Humble study did not have a control group and investigated a range of disorders, not only autism. By contrast, in the Meguid study, vitamin D was measured in an appropriate manner and the recruitment of cases and controls minimised the bias. Taking these studies together, they are suggestive that there may be a link between low vitamin D and autism and this will be an important direction for future research.

There is a fourth study – of mothers of Somali origin with children with autism in Sweden – that is of relevance in the present context (Fernell et al., 2010). This study will be discussed in more detail later but, in brief, mothers of children with autism had the lowest levels of vitamin D. The differences between mothers of Somali origin with and without a child with autism were not statistically significant, but those with a child with autism had approximately 30% lower mean value of vitamin D during spring (the time of lowest availability of vitamin D) compared with those whose child did not have autism. All Somali mothers had vitamin D levels in the deficient range.

3.1.2. Autism – vitamin D: nutritional status, clinical and case studies

It has been suggested that nutritional supplementation before and during pregnancy, including with vitamin D, may prevent some cases of autism, schizophrenia, epilepsy and Parkinson's disease (Johnson, 2001). Vitamin D deficiency and insufficiency is common during pregnancy (Hollis, 2007; Johnson et al., 2011).

Lindsay et al. (2006) used a quantitative 'Food Frequency Questionnaire' (FFQ) to prospectively study the nutritional intake of 20 children (5–13 years old) with autism. The results of this questionnaire study suggested that 50% of these children with autism were likely to have inadequate vitamin D intake.

Several observational and clinical studies reported vitamin D deficiency in children with autism as a consequence of the highly selective eating behaviour that is typical for this group (Clark, Rhoden, & Turner, 1993; Noble, Mandel, & Patterson, 2007; Schreck, Williams, & Smith, 2004; Stewart & Latif, 2008; Weig, 2009). Several studies reported an association between the vitamin D status and nutrition in children or young people with autism (Herndon, DiGuiseppi, Johnson, Leiferman, & Reynolds, 2009; Lindsay et al., 2006; Sadowska & Cierebiej, 2011; Schreck et al., 2004; Shamberger, 2011). Thus, Shamberger (2011) in an ecological study across the 50 United States, showed that infants who were solely breast-fed had diets low in vitamin D and other nutrients and that in states with high rates of exclusive breast-feeding, autism rates were also higher. This would imply the need for vitamin D supplementation during the breast-feeding period.

Herndon et al. (2009) found few differences in average nutritional intake between children with autism and typically developing children in Colorado, USA. However, a large proportion of children in both groups did not meet the national recommendations for daily intake of fibre, calcium, iron, vitamin E and vitamin D. Very similar results have been reported recently by Sadowska and Cierebiej (2011) in Poland.

There are four case studies reporting an extreme form of inadequate nutritional status due to food selectivity and food-avoidant behaviours in children/young people with autism, leading to the symptomatic nutritional rickets or painful leg weakness. In all four cases, severe vitamin D deficiency was diagnosed and the rickets and pain were successfully treated with adequate diet and vitamin D supplementation (Cannell & Hollis, 2008; Clark et al., 1993; Noble et al., 2007; Stewart & Latif, 2008; Weig, 2009). These studies highlight the possibility of acquired hypocalcaemia and hypovitaminosis D in subgroups of children and adolescents with autism and suggest the importance of a comprehensive history-taking, careful diet assessment, and when appropriate, screening for vitamin D deficiencies as an integral part of every child with autism's medical care (Cannell et al., 2008; Holick et al., 2011; Noble et al., 2007).

One of the suggested mediating roles of vitamin D in aetiology of autism is its involvement in absorption of magnesium (Johnson, 2001), one of several important micronutrients, known to have crucial roles in brain development, e.g., preventing oxidative damage. The absorption of magnesium requires adequate levels of parathyroid hormone and vitamin D and may thus be dependent on nutrition as well as season and sun exposure. There have been many studies examining a possible relationship between the month and season of birth and risk for ASD. However, results are diverging as to potential risk period and some authors have found no support at all for the seasonality hypothesis (Gillberg, 1990; Hebert, Miller, & Joinson, 2010; Kolevzon et al., 2006; Landau, Cicchetti, Klin, & Volkmar, 1999; Zerbo, Iosif, Delwiche, Walker, & Hertz-Picciotto, 2011).

3.1.3. Autism – vitamin D: latitudinal effects and ethnicity, clinical studies

Grant and Soles (2009) found a strong latitudinal (related to wintertime solar UVB radiation) increase in infantile autism prevalence. This finding is consistent with the hypothesis of maternal vitamin D deficiency being a risk factor for autism (Cannell, 2008).

Gillberg et al. (1995) reported on 3 boys with autism, born in one area of Sweden and with mothers coming from Uganda, and discussed possible reasons for the high autism rate in this particular ethnic subgroup. Due to an increased prevalence of autism in children of Somali origin living in Sweden, and the evidence that low vitamin D impacts adversely on brain development, serum levels of calcidiol were analysed in mothers of Somali origin with and without a child with autism (Fernell et al., 2010). Since the availability of vitamin D differs across the year, plasma levels were measured in both spring and autumn. Both groups of mothers of Somali origin had significantly lower values of calcidiol compared to Swedish mothers, in both spring and autumn. The difference in the levels of calcidiol between mothers of Somali origin with a child with or without autism was not statistically significant, but the lowest values of all in the study were found in mothers with a child with autism. The authors concluded that the findings regarding very low vitamin D levels generally in Somali mothers have considerable consequences from a public health perspective, and that more research regarding the role of vitamin D in autism is warranted.

A review by Dealberto (2011) summarized several studies reporting on increased rates of autism among dark-skinned immigrant mothers, especially those who moved to high latitudes. The results of this review are consistent with the hypothesis that maternal vitamin D deficiency (or insufficiency) levels may be associated with autism.

In a review on ASD in Africa, Bakare, Munir, and Kinney (2011) pointed out that autism and hypomelanotic disorders (such as albinism) can co-occur. This "co-morbidity" of autism and oculo-cutaneous albinism led the authors to suggest a hypothesis of individuals with hypo-melanotic skin types being genetically more predisposed to autism with an acknowledged modulatory role of vitamin D deficiency. The postulated aetiological factors included post-encephalitic infection, genetic and auto-immune factors, and vitamin D deficiency (Table 2).

3.2. Narrative review

The results in this section will be grouped under four subheadings, related to different aspects of vitamin D and autism: (a) genetics and gene regulation, (b) the brain (homeostasis, neurodevelopment and the brain's own immune system), (c) epilepsy/seizures, and (d) medication in pregnancy.

Table 2
Clinical studies of vitamin D and autism.

Vitamin D and autism – clinical studies	First author	Type of study	Year
Strong effect of latitudinal increase on Childhood Autism prevalence	Grant	Epidemiologic	2009
Nutrition – inadequate vitamin D intake in children with ASD due to their selectivity with food	Sadowska	Clinical	2011
	Schamberg	Clinical	2010
	Herndon	Clinical	2008
	Lindsay	Clinical	2006
Extreme cases of inadequate nutritional intake resulting in co-morbidity of autism and rickets	Weig	Case	2009
	Stewart	Case	2007
	Noble	Case	2007
	Clark	Case	1993
Medication in pregnancy – antiepileptic drugs			
Lower levels of vitamin D observed in babies born to mothers on anti-epileptic drugs during pregnancy	Bromley	Clinical	2009
Ethnicity			
Observed low vitamin D in Somali origin mothers of children with ASD in Sweden	Fernell	Clinical	2010
Increased rates of ASD among dark-skinned immigrant mothers at high latitudes	Dealberto	Review	2010
Plasma levels in children with ASD			
USA	Molloy	Clinical	2010
Egypt	Meguid	Clinical	2010
Plasma levels of vitamin D measured in a group of adult out-patients with various psychiatric illnesses – lowest levels in groups with ASD and schizophrenia	Humble	Clinical	2010

3.2.1. Autism – vitamin D: genetics and gene regulation

The likely causes of ASD involve mutations or common variants in genes, which are involved in (1) cell–cell interaction and synaptic function, including development of dendritic spines, (2) neuronal migration and growth, and/or (3) excitatory and inhibitory neurotransmission (Freitag et al., 2010). Animal research has demonstrated that vitamin D plays a role in all of these brain processes (Almeras et al., 2007; Eyles et al., 2005; Eyles, Burne, & McGrath, 2011; Harms et al., 2011).

Vitamin D exerts its effects on genes through the vitamin D receptor (VDR), which binds to specific locations of the genome to influence gene expression. Employing ChIP-seq technique, Ramagopalan et al. (2010) isolated fragments of genomic DNA bound to the VDR before and after treatment of cells with calcitriol, and then sequenced the DNA fragments. By mapping the sequences back to the genome, the group identified more than 2700 sites of VDR binding, a number showing the importance of vitamin D in human body and also the wide variety of biological pathways in which vitamin D apparently plays a role in. These findings support the hypothesis that vitamin D interacts with genes in the pathogenesis of diseases and suggest the serious risks of vitamin D deficiency (Kalueff et al., 2006; Ramagopalan et al., 2010).

Prenatal vitamin D deficiency or defects in its metabolism can disrupt normal neuro-development as vitamin D plays a role in neuronal growth (Cui, McGrath, Burne, Mackay-Sim, & Eyles, 2007) and in regulating cell proliferation in the developing brain (Eyles et al., 2011). This role is corroborated by detecting calcitriol and its receptors in a variety of brain tissues early in embryogenesis (McGrath, Feron, & Mackay-Sim, 2001).

Recent studies portray the role of signalling pathways in the brain and the synapse structure as crucial to the development of ASD. Most plausible "ASD explanations" posit interaction between underlying genetic and non-genetic biological factors (Currenti, 2010). Interestingly, cytogenetic aberrations in autistic individuals have been located in nearly every chromosome (Gillberg, 1998) (Table 3).

3.2.2. Autism – vitamin D: brain, neurodevelopment, brain homeostasis and the brain's own immune system

Table 3 provides an overview of some of the most important papers published in recent years on the role of vitamin D in brain development and brain functions.

Vitamin D affects numerous neuronal functions and animal studies have demonstrated a specific role in cell differentiation, neurotrophic factor expression, cytokine regulation, neurotransmitter synthesis, intracellular calcium signalling, anti-oxidant activity, and the expression of genes and proteins involved in neuronal differentiation, structure and metabolism (Eyles et al., 2005, 2011).

Animal studies have shown that vitamin D deficiency has a negative effect on embryonic neurodevelopment, manifested, e.g., in decreased neurotrophic factor levels, increased mitosis, and decreased apoptosis, enhanced proliferation, and some changes in the brain morphology and altered behaviour (Eyles et al., 2006; Harms et al., 2011). It is known that microglia contain vitamin D receptors (VDR) and when they are activated (e.g. by interferon-γ), they can actually synthesise calcitriol (d'Hellencourt, Montero-Menei, Bernard, & Couez, 2003; Neveu et al., 1994).

In view of the presence of vitamin D, its activating enzymes, and vitamin D receptors (VDR) in the brain (Eyles et al., 2005), and assuming that they are involved in normal brain functioning, an argument can be made for re-classifying the vitamin D as a neuro-steroid. In addition, the presence of high levels of VDR in the developing brain from very early stages and its increase with gestational age, suggests a role for vitamin D in neurodevelopment (Eyles et al., 2011). It seems reasonable to speculate that vitamin D deficiency during development could be a risk-modifying factor in relation to other factors, such as maternal infection, stress, or neurotoxicity (Bodnar et al., 2007; Cannell, 2008; Grant & Soles, 2009).

Animal studies have shown that early life hypovitaminosis in vitamin D leads to disruption and alterations in brain development (larger lateral ventricles, reduced expression of nerve growth factor (NGF), reduced expression of a number genes involved in neuronal structure or neurotransmission) and that these changes are permanent in the adult brain (Feron et al., 2005).

Numerous studies have shown that vitamin D plays an important role in brain homeostasis. For example, a very high level of activity of the vitamin D specific DNA-response element (VDRE) has been demonstrated in the cerebellum of rats (Taniura et al., 2006), a brain region that has been frequently linked to ASD and other neuro-developmental disorders. Post-mortem human studies have shown that other areas of the brain, e.g., the hippocampus, limbic system, pituitary, substantia nigra, diencephalon, and cerebral cortex and white matter more generally have high concentrations of vitamin D receptor (VDR)

Table 3
Narrative review.

Possible vitamin D involvement in autism via	First author	Type of study	Year
The brain	Harms	Review	2011
	Blaylock	Review	2009
	Lucas	Review	2008
	Lawrence	Original article	2008
Foetal brain development	Eyles	Review	2011
Genetics	Currenti	Review	2010
	Ramagopalan	Original article	2010
De novo genetic mutations	Kinney	Review	2009
Hypomelanosis	Bakare	Hypothesis	2011

and the enzyme necessary for the synthesis of calcitriol (Eyles et al., 2005). In addition, calciferol induces the production of anti-inflammatory cytokines IL-10, IL-4 and TGF-β1. Its deficiency has been shown to result in elevation of glutathione levels, which the brain produces in an attempt to reduce the damaging effects of toxins (Blaylock & Strunecka, 2009). Furthermore, calciferol significantly stimulates the production of glial-derived neurotropic factor (GDNF) and thus serves as a neuro-protective agent (Cantorna, Hayes, & DeLuca, 1996). A recent review suggested that various environmental toxins (including mercury) have a pathological role in initiating and worsening excitotoxicity and brain inflammation and that vitamin D may have a role in ameliorating some of these effects (Blaylock & Strunecka, 2009).

The nuclear receptor for vitamin D has been localized in neurons and glial cells. Vitamin D is involved in the biosynthesis of neurotropic factors and may also be involved in brain detoxification pathways (Garcion, Wion-Barbot, Montero-Menei, Berger, & Wion, 2002). These detoxification pathways include an increase in levels of glutathione, a peptide, whose role is to remove free radicals and to chelate heavy metals, including mercury (Kern & Jones, 2006). Vitamin D also plays a trophic role in the central nervous system (CNS) and protects cultured cortical neurons from glutamate excitotoxicity via up-regulation of the VDR (Blaylock & Strunecka, 2009).

The possible role of hippocampus in ASD has been explored in a number of neuro-imaging and post-mortem brain studies, and several of them have documented certain abnormalities in this limbic structure. One of these studies demonstrated up-regulation of calbindin-immunoreactive hippocampal GABA-ergic interneurons that probably play a role in learning and information processing (Lawrence, Kemper, Bauman, & Blatt, 2010). Calbindin is a family of vitamin D dependent calcium-binding proteins.

3.2.3. Autism – vitamin D: epilepsy and seizures

Animal and clinical studies have demonstrated the neuro-protective role of vitamin D in epilepsy (Harms et al., 2011). As epilepsy and convulsions are very common in autism (Coleman & Gillberg, 2011), it is interesting to note calcitriol's neuro-protective effects via its inhibitory effect on Ca^{2+} influx. Calcitriol up-regulates the expression of the calcium-binding proteins calbindin and parvalbumin in motor neurons (Alexianu, Robbins, Carswell, & Appel, 1998), which chelate intracellular Ca^{2+} and thus limit the excitotoxicity (Harms et al., 2011).

Vitamin D deficiency thus might lead to disruption in calcium signalling and homeostasis, which might account for some pathologies and disrupted information processing typical for autism. Severe calcidiol deficiency has been shown to be associated with seizures caused by disruption of calcium levels (Mehrotra et al., 2010). Vitamin D has also been shown to increase the electroconvulsive threshold for seizures, to decrease the severity of seizures, and to enhance the effect of the antiepileptic medication (Borowicz, Morawska, Furmanek-Karwowska, Luszczki, & Czuczwar, 2007; Kalueff, Minayan, & Tuohimaa, 2005; Siegel, Malkowitz, Moskovits, & Christakos, 1984). The protection against excitotoxicity might also explain the protective action of vitamin D against seizures (Harms et al., 2011). However, antiepileptic drugs are known to decrease vitamin D levels, which further complicate research on the potential link between vitamin D deficiency and increased risk of seizures (Berquist, Schall, & Stallings, 2007).

3.2.4. Autism – vitamin D: medication during pregnancy

Bromley, Mawer, Clayton-Smith, and Baker (2008) reported on low plasma levels of vitamin D and an increased incidence of autism among infants of mothers taking antiepileptic medication, especially sodium valproate, during pregnancy. This finding may suggest low vitamin D levels as a possible mechanism warranting further investigation. An inverse relationship between the antiepileptic drugs and calcidiol levels have been demonstrated in animal research (Borowicz et al., 2007).

4. Discussion

Vitamin D deficiency – either during pregnancy or early childhood – has recently been proposed as a possible environmental risk factor for ASD. A large number of studies support the role of vitamin D in numerous cellular functions, in particular, cell differentiation, neurotrophic factor expression, cytokine regulation, neurotransmitter synthesis, intracellular calcium signalling and anti-oxidant activity. In animal studies its ability to partially reverse brain damage has been demonstrated (Burne, Feron, Eyles, McGarth, & Mackay-Sim, 2004), as well as its ability to increase cellular levels of glutathione (Garcion et al., 2002) and the expression of genes and proteins involved in neuronal differentiation, structure, and metabolism (Eyles et al., 2011). Results of these studies have been translated into theories and hypotheses regarding a possible involvement and role of vitamin D in aetiology and/or phenotype expression of ASD, some more plausible than others. Most of these hypotheses support the notion that neither genetic nor environmental exposure operate alone in the development of autism. Risk factors are likely to involve a combination of genetic susceptibilities and environmental exposures.

The discovery of increased rates of autism in people with darker skin at higher latitudes indirectly provides support for the hypothesis of vitamin D deficiency in the pathogenesis of autism. This hypothesis is also supported by the observation that mothers taking anti-epileptic drugs in pregnancy have babies with lower levels of vitamin D and with higher rates of autism.

Results from on-going research in schizophrenia might provide possible clues to the pathogenesis of ASD as there are some parallels between the aetiology of both disorders and hypothetically both may be related to prenatal and developmental vitamin D deficiency (Grant & Soles, 2009; Humble et al., 2010).

When children with ASD were studied as to nutritional history, they were repeatedly shown to probably have inadequate intake of vitamin D due to their highly selective intake of food. Hence, children with autism are one of the populations that are at a risk of being deficient in vitamin D. Therefore, patients with ASD should have their diet carefully assessed and, when appropriate, screened for vitamin D deficiency as an integral part of the child/patient's medical care (Holick et al., 2011; Noble et al., 2007).

It is important to consider that autism is a very heterogeneous condition with many aetiologies and that vitamin D might be one important factor in the aetiological panorama among other operating elements.

5. Conclusion

Vitamin D deficiency – either during pregnancy or early childhood – has recently been proposed as a possible environmental risk factor for ASD. The findings obtained over the past 15 years, including animal studies, human molecular, cellular and physiologic research, post-mortem brain, neuro-imaging, and genetic studies, suggest that vitamin D plays numerous roles in various processes in the human body. However, the literature is very limited as regards clinical studies of individuals with autism or their close relatives and provides only weak support for the hypothesis of the modulatory role of vitamin D in the pathogenesis of autism specifically. Therefore, there is an urgent need for intensified research in this important area. If pursued with greater detail as regards other environmental variables, medical and family history and genetic analysis, such studies might offer a very valuable insight into this intriguing interplay of genetics, environmental factors, and the proposed role of vitamin D in foetal neuro-development. This approach will require large and comprehensively diagnosed cohorts with ASD, preferably sampled in a population context. There is also a need for more in-depth longitudinal research on chronic latent vitamin D insufficiency and deficiency.

Despite the limited and inconclusive results of this review, there are indications that individuals with ASD may be one of the populations at risk for vitamin D deficiency/inadequacy, and that low vitamin D levels in utero or early postnatal life might interact with other factors to increase the risk for ASD.

Acknowledgements

We acknowledge the valuable assistance of Dr. Helen Marlborough regarding the literature search and the administrative help of Irene O'Neill in preparation of this manuscript.

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